

## REMARKS

Claim 1 is amended herein. Claims 11-22 are canceled without prejudice. Claim 32 is added. Support for the amendments in claim 1 and new claim 32 can be found at pages 2-5 of the specification, particularly the term "micelle" in the last line at page 2, figures 1 and 2, and claim 1 as originally filed. Reconsideration of the outstanding rejections is respectfully requested.

### ***Interview Summary***

Applicants appreciate Examiner Shibuya for the interview, conducted on June 6, 2006 at the USPTO. During the interview, a video animation clip illustrating Mozaic™, which is an embodiment of the claimed invention, was shown. A powerpoint printout related to Mozaic™ were also presented and the basic concept of the invention was explained. A potential claim amendment specifying the non-covalent association as a micelle was discussed in the context of overcoming the cited prior art references, and a lipid bilayer structure was distinguished from a micelle structure. Various possibilities of the use of the claimed composition were also explained, including facilitating drug delivery with the micelle structure. It was also explained that there is no need to know the actual structure of a ligand to practice the current invention. Further, it was explained that an advantage of the invention is that no prior knowledge of the exact structure of the ligand is necessary to determine a preferred composition of the head groups. The current invention was distinguished from a traditional microarray. The difference between "capping" caused by antibodies and the current invention was also discussed. Applicants volunteered to provide the examiner with a summary of the difference between the "capping" and the current invention.

The capping phenomenon is one where a cell surface protein embedded within the outer membrane of a cell is cross-linked by antibody molecules, which causes the protein to aggregate and then migrate to one end of the cell, forming a structure called a cap. In capping, the cell surface molecule cross-linked by antibodies have more than two epitopes in each of the cell surface molecules so that each surface molecule can bind to at least two antibody molecules (ligands). Further, in capping cell surface molecules do not interact with each other to form an epitope for binding to a certain antibody.

In contrast, no head groups bind to more than one ligand in the current invention. The head groups of the current invention non-covalently associate with one another to form an

epitope which binds more strongly than each of the head groups individually does. The epitopes formed by the head groups of the current invention are the result of non-covalent association of the conjugates, forming the micelle structure and presenting the head groups on the surface of the micelle.

Also, in capping, the surface molecules have to migrate around the cell to finally aggregate to form the cap, whereas in the current invention, the head groups already substantially cover the surface of the micelle with various combinations of the head groups as a result of the conjugates (comprising the head groups and hydrophobic tail groups) forming a micelle structure. Therefore, in the current invention some of the head groups are already appropriately positioned to form an epitope which binds to a ligand.

Further, in the present invention, the ligand does not need to bind first to one headgroup, then stay stuck to the head group while it finds another which can also fit into its binding site. In the present invention, the head groups bind to the ligand as a single unit, substantially all at the same time. In contrast, in lymphocyte capping, the surface proteins are usually separate from each other, and the antibody binds first to one protein, then migrates over the surface until it finds another protein to which it can bind, and which may already be bound to something else.

***Priority***

A certified copy of the United Kingdom Application No. 9915074.0 is provided herewith.

***IDS***

Two US family members of EP 0338437 are provided in the concurrently filed IDS.

***Sequence Listing***

The previous sequence listing filed on February 22, 2005 was rejected because of the description of artificial sequences. Applicants submit that the current application does not need a Sequence Listing. The consecutively listed amino acid symbols in the tables on pages 17, 18, 21 and 23 do not represent peptide sequences. They merely indicate the types of head groups of specific embodiments. For example, "EYQS" indicates that four conjugates are present, in which one conjugate has glutamic acid as the head group, a second conjugate has tyrosine as a head group, a third conjugate has glutamine as a head group and the fourth conjugate has serine as the head group. An amendment to the specification deleting the unnecessary sequence identifiers and the Sequence Listing were made herewith.

***Claim Rejections 35 USC §112***

Claims 1-12 were rejected under 35 USC §112 as failing to comply with the written description requirement. As an initial matter, it is noted that claims 11 and 12 have been canceled without prejudice.

The Examiner contended that "[t]he skilled artisan cannot envision the detailed chemical structure of the encompassed genus of head groups that will interact with any signal ligand, and cannot envision that applicants possessed the claimed composition for use as drugs, prophylactics and diagnostics, as contemplated in the specification and claimed in claim 12." The Examiner further contended that "[t]he specification does not describe any particular molecules, other than amino acids and peptides, that elicit a biological response, and so by extension, may be binding to ligands...[and t]he identity of these ligands is not described." The Examiner also contended that "[a]pplicants have not described a sufficient number of species of head groups that bind to the vast genus of ligands, including various cell surface receptors, small molecule drugs, nucleic acid sequences, etc."

It is submitted that a number of different classes of head groups are described in the paragraph bridging pages 3 and 4. These classes include an amino acid or peptide; a peptide analogue; a mono-, di- or poly-saccharide; a mono-, di- or poly-nucleotide; a sterol; an alkaloid; an isoprenoid; an inositol derivative; a single or fused aromatic nucleus; a water-soluble vitamin; a porphyrin or haem nucleus; a phthalocyanine; a metal ion chelate; a water-soluble drug; a hormone; or an enzyme substrate. One skilled in the art would know what individual species of chemical compounds are described as the head groups of the claimed invention from the genres disclosed. Moreover, the applicant has provided sufficient disclosure for the skilled person to identify other suitable head groups. As set out in the application in the paragraph bridging pages 8 and 9 and in the following paragraph on page 9, various ways are available for selecting the head group of the conjugates. This provides the skilled person with a representative number of different types of head groups which could be used in the composition according to claim 1.

The applicant has also shown reduction to practice for a large number of compositions with amino acid head groups, which form epitopes capable of interacting with the ligand more strongly than each of head groups individually. For example, the combination of head groups Y and Q; Y and S; Y, S and H; E, Y and S; and E, Y, Q, and S are disclosed in the table of page 18. The combinations of head groups L and S; L and E; L and Q; S and E; S and Q; E and Q; L, S and E; L, S and Q; L, E and Q; S, E and Q; and L, S, E and Q are disclosed in the table at

page 23. Y, F and L; Y, W and L; and F, W and L are disclosed in the table at page 26. All these head group combinations show a stronger effect on the target cell in the specific combinations than the head groups of the combinations individually do.

Further, it is submitted that the nature of the invention and, in fact, the advantage of the invention is that one skilled in the art does not need to have the knowledge of the specific structures of the head groups or ligands to practice or describe the claimed invention. The composition of claim 1 allows the skilled person to elucidate what combination of head groups is capable of forming an epitope to a given ligand of biological interest, without the need to link all possible combinations of those building blocks together in all possible ways by chemical means. The composition thus allows a novel method of constructing a library of different epitopes, which can be tested using a biological assay directed to a desired biological effect. The combinatorial nature of the composition makes it unnecessary and impracticable to specify only a couple specific chemical compounds, moieties or residues as suitable for binding to a certain ligand. Any head group may be suitable in any given situation and this will depend upon the target ligand. Unlike a traditional chemical compound genus, wherein the use of the genus is implemented through a very limited number of selected species, in the current invention, the genus is useful as the genus itself, not only by a few selected species from the genus. As explained during the interview, and also illustrated by the attached Powerpoint printout relating to Mozaic™,<sup>1</sup> various combinations of a substantial number of distinct head groups can be screened for a specific combination of distinct molecules including amino acid, peptides, nucleotides, aromatic rings and so on, by comparing biological effects of various combinations of head groups.

For example, at page 18 of the instant application, the head groups E,Y,Q,S, and H are screened for biologically the most effective combination using five sets of combinations of head groups, generated by taking out a head group from the five head groups for each set. Comparing the assay result of the five sets (i.e., EYQS, EYQH, EYSH, EQSH and YQSH), one would find EYQS combination set is biologically more effective than any other in the five sets. Then, one can narrow down the screening to four combinations of YQS, EYS, EYQ and EQS, and one would find EYS has the highest biological effect so far. One can still divide the EYS

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<sup>1</sup>With respect to the Powerpoint printout, Applicants note that pages 6, 9-12 and 37 have been excluded. These pages relate to additional technology which is not part of the present invention and confidential.

into EY, ES, and YS combinations and find that still EYS combination has the highest biological effect. While selecting this EYS through the combinatorial screening method using the claimed compositions of the invention, the entire spectrum of the genus was useful to pinpoint the specific EYS combination. Therefore, the usefulness of the invention substantially stems from the existence of the genus itself. Therefore, in view of the combinatorial nature of the invention, it is submitted that the general genus description of the invention provides an adequate written description support for the invention.

With regard to the contention that the identity of ligands were not described, it is submitted that it is not necessary to describe the exact chemical structure of a ligand to adequately describe the invention because the present invention allows the construction of an epitope from a wide range of head groups without the need to know the exact chemical structure of the target ligand. As explained above, different combinations of conjugates incorporated into micelles can be easily produced and a biological response thereto can be measured to determine the existence and strength of ligand epitope interaction. In fact, the ligand is not a part of the claimed composition.

With regard to the contention that the specification does not describe actual binding to any particular ligand, it is submitted that a known biological activity of the target ligand can be and in fact is routinely used to confirm the actual binding of the composition to a target ligand. The specification in examples, 1, 3 and 4 show three separate compositions demonstrating epitope ligand interactions in three completely separate biological tests and therefore, and therefore, the specification does describe actual binding to ligands.

Further, the breadth of the claims is fully justified in view that the present invention opens up a whole new field of combinatorial chemistry

For the reasons set forth above, it is submitted that the written description rejection is overcome, and withdrawal thereof is respectfully requested.

### ***Indefiniteness***

It is submitted that the indefiniteness rejection based the claim language "wherein in tail groups" in line 3 and "a ligand" in line 5 of claim 1 is obviated by the amendment in claim 1.

With regard to the term "more strongly," it is submitted that the skilled person would easily be able to understand the claim language "at least two head groups interact with the ligand more strongly than each of the head groups individually" is showing higher measurement values of desired biological effects, for example, higher measurement results from the assays

described on page 8 of the specification as filed and using experimental methods well known in the art. Therefore, the term "more strongly" is not indefinite.

It is also submitted that the skilled person would clearly understand the term "analogue" in the context of "peptide analogue" and "lipidic amino acid analogue" to mean any structurally related peptide or lipidic amino acid with the same function because the term is well known to the skilled person in these contexts. Therefore, one would know the scope of protection conferred.

For the reasons set forth above, it is submitted that the indefiniteness rejection is overcome, and withdrawal thereof is respectfully requested.

### ***Prior Art***

Claims 1-12 were rejected under 35 USC §102 as being anticipated by Crabtree et al., Capon et al., Ueda et al. or Toth et al. As an initial matter, it is noted that claims 11 and 12 were canceled without prejudice.

### **Crabtree**

Crabtree et al. disclose chimeric (or "fused") proteins, DNA constructs encoding them and ligand molecules capable of oligomerizing the chimeric proteins. The chimeric proteins contain at least one ligand binding (or "receptor") domain fused to an action domain capable of initiating apoptosis within a cell (see page 3). The oligomerizing ligands are capable of binding to two or more of the receptor domains i.e. two or more chimeric proteins containing such receptor domains (see page 4). The encoded chimeric protein may comprise an intracellular targeting domain capable of directing the chimeric protein to a desired cellular compartment (see page 4). The targeting domain can be secretory leader sequence, a membrane spanning domain, a membrane binding domain or a sequence directing the protein to associate with vesicles or with the nucleus, for instance (see page 4).

The Examiner contends that the chimeric proteins disclosed in Crabtree et al. reads on the conjugates of claim 1, the receptor domains of the chimeric protein reads on the head group of claim 1 and the intracellular targeting domain reads on the tail group of claim 1. The Examiner further contends that the chimeric proteins are movable by virtue of the transmembrane within the cell and this reads on the feature that wherein in the presence of a ligand at least two of the head groups are appropriately positioned to form an epitope capable of interacting with the ligand more strongly than each of the head groups individually.

Each chimeric protein of Crabtree et al. contains at least one receptor domain which binds to a ligand on its own without any interaction with other chimeric proteins. Crabtree et al. do not teach or suggest a composition wherein receptor domains of different chimeric proteins are appropriately positioned to form an epitope capable of interacting with the ligand more strongly than each of the receptor domains individually.

Amended claim 1 is further distinguished from Crabtree et al. due to the recitation that "the non-covalent association comprises a micelle." Crabtree et al. do not teach or suggest a micelle of the chimeric proteins. The Examiner contended that Crabtree et al. disclose that the chimeric proteins may be expressed in a cell and the cell reads on a lamellar structure, micelle or liposome. However, it is submitted that a cell membrane is a phospholipid bilayer whereas a micelle comprises a single layer of, for example, phospholipids with the phospholipid hydrophilic heads on the outside and the hydrophobic tails pointing in.

For the reasons set forth above, it is submitted that the anticipation rejection over Crabtree et al. is overcome, and withdrawal thereof is respectfully requested.

#### Capon

Capon et al. disclose chimeric proliferation receptor proteins and DNA sequences encoding these proteins (see page 6). The chimeric proliferation receptor proteins comprise at least an extracellular inducer responsive clustering domain that binds to an extracellular inducer, a transmembrane domain that crosses the cell membrane and a cytoplasmic proliferation signalling domain that signals the cell to divide upon the clustering of the extracellular domains (see page 3). The chimeric proliferation receptor proteins may also have an effector function signaling domain between the transmembrane domain and the proliferation signaling domain or it may be attached to the C-terminus of the proliferation signaling domain (see page 3). The extra cellular inducer responsive clustering domain or ECD refers to the portion of the protein which is outside the plasma membrane of a cell and binds to at least one extracellular inducer molecule (see page 6). After binding one or more inducer molecules, the ECDs become associated with each other by dimerization or oligomerization (see page 7). Each inducer molecule or group of inducer molecules is presented multivalently (e.g. more than one inducer molecule in close proximity to each other on a cell surface) to the receptor protein. The inducer molecules will thus bind more than one ECD, causing the ECDs to dimerize or oligomerize (see page 11). This clustering transmits a signal through the transmembrane domain to the proliferation signalling domains, which become activated.

The Examiner contends that the inducer disclosed in Capon et al. reads on the ligand in claim 1, the chimeric receptor proteins reads on the conjugate in claim 1, the extracellular inducer binding domain reads on the head group in claim 1 and the transmembrane domain and cytoplasmic effector function signaling domain reads on the tail group according to claim 1. The Examiner further contends that the transmembrane domain and cytoplasmic effector function signaling domain would inherently form a hydrophobic aggregation with the conjugates movable within the association so that in the presence of a ligand at least two of the head groups would be appropriately positioned to form an epitope capable of interacting with the ligand more strongly than each of the head groups individually.

Applicants respectfully traverse. The extracellular inducer binding domains of separate receptor proteins do not appropriately position to form an epitope capable of interacting with a ligand more strongly than each inducer binding domain individually. Capon et al. clearly disclose that each inducer binding domain binds to an inducer molecule which also binds to other inducer binding domains of separate receptor proteins. This binding causes the inducer binding domains to dimerise or oligomerise but the separate inducer binding domains do not cooperate to form an epitope.

Amended claim 1 is further distinguished from Capon et al. due to the recitation that "the non-covalent association comprises a micelle." Capon et al. do not teach or suggest a micelle of the chimeric proteins. Capon et al. disclose host cells bearing the chimeric proliferation receptors, and as explained above with regard to Crabtree et al., a cell is not a micelle.

For the reasons set forth above, it is submitted that the anticipation rejection over Capon et al. is overcome, and withdrawal thereof is respectfully requested.

#### Ueda

Ueda et al. disclose a pair of chimeric polypeptides anchored in the plasma membrane, each of which has a variable region sequence and an effector sequence (see abstract). The polypeptides are independent in the absence of antigen, but form a stable complex with each other when antigen is provided (see abstract). Each polypeptide comprises an extracellular domain comprising a variable domain sequence, a transmembrane domain and an effector sequence (see paragraph [0019]). Upon expression of the two polypeptides in a host cell, contacting the cell with an analyte promotes the association of the variable domain sequence of the first polypeptide with the variable domain sequence of the second polypeptide, thereby promoting the association of the effector sequence of the first polypeptide with the effector

sequence of the second polypeptide and inducing a change in cell phenotype (see paragraph [0019]). Preferred variable region sequences are complimentary  $V_H$  and  $V_L$  sequences (see paragraph [0019]). Ueda et al. disclose host cells expressing the chimeric polypeptides of the invention (see paragraph [0020]). Ueda et al. disclose at paragraph [0062] that a transmembrane domain is included to keep each of the chimeric polypeptides anchored in the membrane and permit lateral movement in the lipid bilayer. It is also disclosed that the transmembrane domain is sufficiently lipophilic to penetrate the lipid bilayer and keep the entire polypeptide inserted in the membrane in a stable fashion.

The Examiner contends that the variable domain sequence in Ueda et al. reads on the head group of claim 1 and the effector sequences and transmembrane sequences read on the tail group of claim 1, the transmembrane domains of the separate chimeric polypeptides disclosed in Ueda et al. form a hydrophobic aggregation as required by claim 1. The Examiner further contends that the chimeric polypeptides are moveable within the association so that in the presence of a ligand at least two of the variable domain sequences are appropriately positioned to form an epitope capable of interacting with a ligand more strongly than each of the variable sequences individually.

While Ueda et al. disclose that the chimeric polypeptides form a stable complex with each other when antigen is provided and the variable region sequences may be complimentary  $V_H$  and  $V_L$  sequences, Ueda et al. do not disclose that the variable region sequences are appropriately positioned to form an epitope capable of interacting with a ligand more strongly than each variable sequence individually. In Ueda et al., the variable sequences of each polypeptide associate. However, this does not mean that the two polypeptides form an epitope. Rather, a part of each of the two polypeptides in Ueda et al. bind to the antigen, which brings the two polypeptides together to form the complex. Particularly, paragraph [0049] of Ueda et al., which the examiner relies on, refers to dimerization of the subunits upon binding of the ligand to an extracellular component of the receptor and teaches that the dimerization results from conformational change induced by binds, subunit aggregation induced by multiple ligands or a polyvalent ligand, which binds to each subunit and brings the subunits together. This paragraph does not teach or suggest that the variable regions of each receptor protein cooperatively form an epitope capable of interacting with the ligand more strongly than each of the head groups individually.

Further, claim 1 as amended is further distinguished from Ueda et al. The Examiner contends that the disclosure in Ueda et al. that the chimeric polypeptides may be expressed in a cell reads on a lamellar structure, a micelle and a liposome. As explained above with regard to Crabtree et al., a cell is not a micelle.

For the reasons set forth above, it is submitted that the anticipation rejection over Ueda et al. is overcome, and withdrawal thereof is respectfully requested.

Toth

Toth et al. disclose peptide compounds which comprise a lipophilic anchor section formed from at least one fatty amino acid moiety and a matrix core section having at least four amino acid functionalities, which are the same and selected from the group consisting of  $-NH_2$ ,  $-COOH$ ,  $-SH$ ,  $-OH$  and derivatives thereof (see column 1). Pharmaceutically active moieties, especially peptide antigens, can be bound to the amino acid functionalities for use as, for instance, vaccines and diagnostic agents. The lipophilic anchor allows the compound to be incorporated into lipid vesicles and/or cell membranes (see column 1).

Firstly, Toth et al. does not disclose a non-covalent association of a plurality of distinct conjugates, each conjugate comprising a head group and a tail group. It is clear from figures 1-3, column 3, line 62-column 4, line 1 and column 9, lines 13-21 that the peptide groups referred to in Toth et al. are covalently linked to one compound in n levels in a branched structure. Toth et al. do not disclose or even suggest a composition comprising a non-covalent association of a plurality of distinct conjugates, as required by claim 1.

Secondly, Toth et al. do not disclose that the tail groups of the distinct conjugates form a hydrophobic aggregation. It is clear from figure 1 that the lipid anchor may contain three fatty acid residues which may be incorporated into a lipid bi-layer wall of a liposome. However, Toth et al. do not teach or suggest that tail groups on distinct conjugates form a hydrophobic aggregation.

Thirdly, it is submitted that Toth et al. do not disclose that the conjugates are movable within an association so that in the presence of a ligand at least two of the head groups are appropriately positioned to form an epitope capable of interacting with the ligand. Toth et al. do not disclose that peptide head groups are positioned to form an epitope capable of interacting with a ligand. In contrast, Toth et al. teach that pharmaceutically active substituents are attached to the peptide compound, which may be a drug molecule. It is further taught that the peptide compound may be presented in the form of a liposome composition, which comprises

the new compound anchored in a lipid vesicle via the lipophilic anchor, and the pharmaceutically active substituent may be on the surface of the lipid vesicle or in the intra-vesicular space. Therefore, it is clear that the compound disclosed in Toth et al. functions as an epitope to a ligand on its own without any co-operation with the head groups of other compounds.

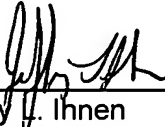
Fourthly, claim 1 as amended recites that the non-covalent association of the conjugates is a micelle. The Examiner contends that Toth et al. teach that the lipid anchors will incorporate into liposomes or cell membranes. As explained above with regard to Crabtree et al., a cell is not a micelle. Also a liposome or a lipid vesicle is not a micelle.

For the reasons set forth above, it is submitted that the anticipation rejection over Toth et al. is overcome, and withdrawal thereof is respectfully requested.

Claim 32 is submitted to be patentable for the same reasons set forth above.

In view of the foregoing, Applicant submits that all pending claims are patentable and the present application is now in condition for allowance.

Respectfully submitted,



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